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10/077,150	02/15/2002	Bernhard Peter Neumann	4-30361B/C1	5272

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EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/077,150	B.P.Neumann
Examiner	**Art Unit**
SUDHAKER PATEL,D.Sc.Tech.	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 22, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above, claim(s) *2* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1 and 3-10* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *09/601,463* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4*
4) ☒ Interview Summary (PTO-413) Paper No(s). *6*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Office Action Summary

Application No.	Applicant(s)
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- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

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Disposition of Claims

4) ☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *1-6 and 10* is/are allowed.

6) ☒ Claim(s) *7-9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *09/601,463* .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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4) ☒ Interview Summary (PTO-413) Paper No(s). 6
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 5 dated 4/22/03 is acknowledged.

Claims 1,2,4,5,10 are related to compound of Formula I of claim 1. Claim 3 is related to a process of making compounds of Formula I. Claim 6 is related to pharmaceutical composition. Claims 7,8,9 are related to use of compounds of claim 1. Therefore, the claims in this application are the claims 1-10.

I. *Election/Restriction*

Applicants' remarks and suggestions are considered , and found persuasive. As the instant application is a CON of U. S. Application Sr. NO. 09601463 filed 10/31/2000 which was abandoned, the examination will be as set forth in M.P.E.P. 803.02. Accordingly, the earlier restriction /election which was as per PCT rules, is withdrawn.

A telephone call was made to Dr. Borovian on 5/7/03(Tel. 908 522 6921) to request an oral election of the species, and applicants confirmed the election of species without traverse of Example 41 which is covered by claim 10(see interview summary enclosed with this communication).

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for examination. Portion of MPEP is provided for convenience:

As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D,

and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the nonelected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the rejected claims would be made final.

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species of Example 41 as recited in claim 10 has following meaning for variables in the generic Formula I of claim 1:

X =-CH=CH- i.e. will provide a bicyclic fused ring with a combination of 6:6 wherein one ring is benzene and the other is heterocycle having 1,4-diazine core which represents a Quinoxaline core;

R1 =6-chloro;

R2 =8-methyl;

"Het" = compounds represented by a radical (a) Formula wherein 1,3-diazine

i.e. pyrimidine ring having R3, R4,-NH-, and-NR5R6 substituents;

R3 =2-methyl;

R4 = 5-methyl;

-NH- = 4, -NH- ;

-NR5R6 =6-substituted amino wherein R5 = n-propyl & R6 = -CH2-Cyclopropyl.

Initial search did not revealed prior art(s).

As per the guide lines above, the search was expanded to all of compounds of Formula I of generic claim 1 wherein X =O, S, N-CH3 or -CAlk=CAlk.

No prior art was found. Therefore, restriction election is now held withdrawn.

First action on merits follows.

II. *Claim Rejections - 35 U.S.C. § 112*

Claims 7,8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

Claims 7,8 provide for the use of the compound , but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 7,8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 9 is recited as:"treatment of any state with increased endogenous level of CRF or which the HPA is disregulated...". Correction to :"treatment of any state with increased endogenous level of CRF or **in** which the HPA is disregulated..." is required.

III. ***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating headache, does not reasonably provide enablement for Alzheimer's disease, Parkinson's disease, cancer, neurodegenerative diseases and others as claimed herein(see page 7 lines 3-14). Claim 9 embraces multitude of disease states under the recitation "Treatment of any state". Also, on page 8 lines 6-11 indicate that the compound of Example 1 exhibits biological activity which include: " exhibition of CRF1 antagonist activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. .

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: **1)**. The nature of the invention, **2)**. the state of the prior art, **3).** the predictability or lack thereof in the art, **4).** the amount of direction or guidance present,

5). the presence or absence of working examples, 6). the breadth of the claims, and 7). the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn in part to treating of diseases caused by neurodegeneration, inflammation, HIV infections, drug addiction, stroke, drug and alcohol withdrawal symptoms, sleeping disorders, Alzheimer's disease, Parkinson's disease, head trauma, fertility, sexual dysfunction and pre term birth and other diseases related to CRF activity, HPA disregulated state, state facilitated by CRF

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat Alzheimer's disease nor is there any compound that can be used to treat drug addiction, drug and alcohol withdrawal symptoms by a single compound. For example, the notion that a compound could be effective against chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances" generally. That is because "chemical substance/drug abuse or withdrawal caused by the cessation of intake of chemical substances" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine,

opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed. Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces disease that are not related or even "opposites"; headache, arthritis and asthma are covered and diseases that are not treatable pharmacologically are also embraced (e.g. cancer, HIV infections).

3) The predictability or lack thereof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the diseases which are responsive to the activity of nicotinic ACh receptor modulators. There is no evidence of record which would enable the skilled artisan in the identification of the diseases treatable with the disorders claimed herein.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present for treatment of the disorders recited.

6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment is unknown.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following reference is cited to show the state of art related to Alzheimer's disease:

Coyle et al(Science Vol.219, pages 1184-1190(1983)) cites in the summary that:" These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory". The authors conclude (see page 1189) that:" The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders".

Specification in pages 6-7 describe various assays and test methods for compounds of Formula (I) which are expected to exhibit CRF antagonistic activity, and further state that the utility of the compounds of invention in the above indicated diseases could be confirmed in a range of tests as stated.. The results and data

obtained thereby will serve the purpose of preliminary screening of the compounds and not for treating the various diseases.

Claim 9 as recited includes: " treatment of any state with increased endogenous level of CRF or which the HPA is disregulated, or of a disease induced or facilitated by CRF". There is no data for " or which the HPA is disregulated state".

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claim.

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a single compound for a method of treating any and all viral infection(s). Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has been achieved, In re Ferens, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, Genentech vs. Novo Nordisk, 42 USPQ 2nd 1001, 1006.All available antiviral/anti-herpes virus drugs to treat viruses could be used in a limited way, and provide protection mostly in combination with other known anti-viral agents having many side effects.

IV. ***Conclusion***

Claims 1-6,10 are allowed.

The closest prior art reference Whitten et al(J. Of Med. Chem.,39/22,4354-4357(1996), also cited as Chemical Abstract DN 126:18845). teaches making of a compound with a core:

"Benzo-thiadiazole-NH-1,2,5-triazine substituted by Me and NH-phenyl groups".

The reference does not teach or indicate to arrive at the instant compounds wherein sulfur has been replaced by, oxygen, N-CH3 , -CH=CH- or -Calk = Calk.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc. Tech., whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703)308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Mukund J. Shah

Mukund Shah

Supervisory Patent Examiner

Art Unit 1624

sp

May 8, 2003

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) (in part) 1-9, drawn to compounds, simple composition, a method of use, and the first recited process of making of Formula I of generic claim 1 wherein X = O or S.

Group II, claim(s) (in part), drawn to compounds, simple composition, a method of use, and the first recited process of making of Formula I of generic claim 1 wherein X = -N-CH3.

Group III, claim(s)(in part)1-9, drawn to compounds, simple composition, a method of use, and the first recited process of making of Formula I of generic claim 1 wherein X = -CH=CH -.

Group IV, claim(s)(in part)1-9, drawn to compounds not included in above groups I-III. If this group is elected further restriction/election will be required, and a single specific species representing the group must be provided as there are many unknowns.

Applicants are required to elect one of the above groups and also a single species in reply to this Office Action.

2. The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They represent different structures.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

The values as presented for Het, together with variables R1, R2, and X will provide multiples of compounds.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

4. The claims are deemed to correspond to the species listed above in the following manner:

When Het = Figure (a)-(c), (d), (e), (f), (g), (h),)I),(j), (k), (l), (m),, (n), (o), etc. together with R1-R8 where applicable, will provide many species.

The following claim(s) are generic: Claims 1,3,9.

5. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The base core Benzo-thiadiazole or Benzo-oxadiazole are known molecules.

6. During a telephone conversation with Mr. J. J. Borovian on 2/12/01 a provisional election was made with traverse to prosecute the invention of Group I, claims(in part) 1-9, and also election of species as presented by Claim 2 and Example 2 as cited on page 10 of the specification. Affirmation of this election must be made by applicant in replying to this Office action. Since claims 1-9 link with other inventions, this application will be examined bearing in mind the subject matter and species as elected by the applicants only. Applicants are urged to limit the scope of the claims, and also check the claim dependency in reply to this Office Action.

Claim Rejections - 35 U.S.C. § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 7-8 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a method or process asserted utility or a well established utility.

Claims 7-8 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a method or process of use asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 U.S.C. § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter which applicant regards as the invention.

a). In the generic claim 1 the compound is presented as: "in free base or acid addition salt" form. The term "acid addition salt" is indefinite because we are not exactly told about the nature of acid. Also, -N+ - O - represents a salt link. Applicants remain silent about their intentions.

B). The process claim 3 does not recite any specifics of the synthesis and is therefore indefinite.

C). Claim 4 presents the compound of claim 1 as: "pharmaceutical" which is indefinite because we are not exactly told about the same.

D).The method for the treatment claim 9 is indefinite because we are not exactly and definitely told about:"state with increases endogenous level of CRF or in which the HPA is disregulated or of a disease induced or facilitated by CFR in a subject....".

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, para one because the specification is non-enabling as a method of making/using a single compound of the invention of the generic Formula (I) of claim 1 where in X = O/S Het = Formulae (n), (p), (l) all representing heterocyclic ring(s) or their composition, or derivatives for making a pharmaceutical from of the compound in free base or acid addition salt form, and a generic method of treatment of any state with increased endogenous level of CRF in a subject. Most of the compounds have : ***substituted oxa-diazole or thia-diazole*** fused with benzene core common, whereas the claim language include multiples of variations in heterocycle attached to these cores etc. in the generic claim 1.

1). The scope of "composition(s) containing a binder to CRF receptor activity is not adequately enabled. There is no guidance as to which components would be suitable for instant compositions for treatment of a subject suffering from a physiological condition(s) related to treatment of any state with increased endogenous level of CFR receptor activity.

Therefore, more than minimal routine experimentation would be required to determine which combination will be suitable for the instant invention since devising a composition or a pharmaceutical for treating any state with increased endogenous level of CRF or in which HPA is disregulated or of a disease induced or facilitated by CRF in a subject is not a minor matter as any textbook on a pharmaceutical, with one or more CFR receptor antagonizing agents will confirm. Furthermore, side effects if any are not disclosed.

The specification is silent regarding the making and using of the additionally claimed compounds/compositions, for treatment of a disease induced or facilitated by CRF which involve physiological conditions in a generic subject etc.. With regard to "how to use", see re Lund 153 USPQ 625.

2).In cases directed to chemical compounds which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

3). "Acid addition salt" as recited in the claims reads on all such moieties regardless of complexity of structure and point of attachment to the heterocyclic core for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present with organic or inorganic-acids or by other process e.g. making of -N-O chain. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1,3(or claims dependent on these claims)

and/ or composition in its "salt form" in combination with other salt etc. as recited herein. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their combinations either alone or in making a pharmaceutical as outlined above, will have ability to generate the compounds in vivo or in vitro by one or more processes.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:*(1).* The nature of invention;*(2).* the state of prior art ;*(3).* the predictability or lack thereof in the art; *(4).* the amount of direction or guidance present;*(5).* the presence or absence of working examples;*(6).* the breadth of the claims, and *(7).* the quantity of experimentation needed.

The claims are drawn to compounds, compositions and method(s)(but not limited to) of antagonizing a CFR receptor in a subject, and the process of making the same.

1). The nature of the invention: The compounds and method of use claim(s) are drawn in part to method treatment of any and all kinds of diseases related to CRF receptor activity, and a wide variety of diseases, the treatment of which can be effected or facilitated by antagonizing CFR.

2). The state of prior art: There are no known compounds of similar structure which have been demonstrated to treating diseases induced or facilitated by CRF in a subject comprising administering to such a subject a therapeutically effective amount of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form.

3). The predictability or lack thereof in the art: It is presumed in the treatment of the subject(s) suffering from a physiological condition(s) e.g. disease induced or facilitated by CRF as claimed

there is a way of identifying those subjects who may develop any kind of physiological conditions including (but not limited to) a single disease. There is no evidence of record which would enable the skilled artisan in the identification of the subjects who have the potential of becoming afflicted with the physiological conditions claimed herein.

4). The amount of direction or guidance present and 5). The presence or absence of working examples: There are no doses present to direct one to protect a potential host from the diseases of various types associated with CRF activity.

6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to) generically any state with increased endogenous level of CRF or in which HPA is disregulated or of a disease induced or facilitated by CRF in a subject etc. which are not related and whose treatment(s) is unknown.

7). The quantity of experimentation need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.